UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,498	03/28/2002	Martin Alan Lee	41577/272081	9595

7590 07/31/2006

John S Pratt
Kilpatrick Stockton
Suite 2800
1100 Peachtree Street
Atlanta, GA 30309-4530

EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 07/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,498	LEE ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *34 and 35* is/are allowed.

6)☒ Claim(s) *1-6 and 8-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to the Amendment received on January 17, 2006 and the response received on September 6, 2005.[1]

Preliminary Remark

Claim 7 is canceled.

Claims 1-6 and 8-35 are pending and are under prosecution herein.

Applicants are reminded that the amendment to the specification made in the Response received on September 6, 2005 has not been entered as the Amendment was non-compliant.

Applicants are requested to submit the amendment to the specification in their next response.

Claim Rejections - 35 USC § 103

The rejection of claims 1-5, 8, 14-16, 18, 25, and 26 under 35 U.S.C. 103(a) as being unpatentable over Beutler et al. (U.S. Patent No. 5,234,811, issued August 10, 1993) in view of Kris et al. (U.S. Patent No. 6,238,869 B1, issued May 29, 2001, filed June 21, 1999) as evidenced by Heritz et al. (Journal of Urology, 1997, vol. 158, no. 6, pages 2291-2295), made in the Office Action mailed on June 1, 2005 is withdrawn in view of the Amendment received on January 17, 2006.

Specifically, the rejection is withdrawn in view of Applicants' specific arguments drawn to the fact that none of the references of record discloses a disposable unit having reagent wells of up to 1000 microns in depth defined between a thermally conducting layer and a facing layer.

The rejection of claim 6 under 35 U.S.C. 103(a) as being unpatentable over Beutler et al. (U.S. Patent No. 5,234,811, issued August 10, 1993) in view of Kris et al. (U.S. Patent No. 6,238,869

[1] The response received on September 6, 2005 had been held non-responsive due to formality. The present Office Action addresses the arguments presented in the response received on September 6, 2005 in connection with the

B1, issued May 29, 2001, filed June 21, 1999) as evidenced by Heritz et al. (Journal of Urology, 1997, vol. 158, no. 6, pages 2291-2295), as applied to claims 1-5, 8, 14-16, 18, 25, and 26 above, and further in view of Moss et al. (U.S. Patent No. 5,386,021, issued January 31, 1995), made in the Office Action mailed on June 1, 2005 is withdrawn in view of the Amendment received on January 17, 2006.

Specifically, the rejection is withdrawn in view of Applicants' specific arguments drawn to the fact that none of the references of record discloses a disposable unit having reagent wells of up to 1000 microns in depth defined between a thermally conducting layer and a facing layer.

The rejection of claims 19 and 20 under 35 U.S.C. 103(a) as being unpatentable over Beutler et al. (U.S. Patent No. 5,234,811, issued August 10, 1993) in view of Kris et al. (U.S. Patent No. 6,238,869 B1, issued May 29, 2001, filed June 21, 1999) as evidenced by Heritz et al. (Journal of Urology, 1997, vol. 158, no. 6, pages 2291-2295) as applied to claims 1-4, 8, 14-16, 18, 25, and 26 above, and further in view of Little et al. (U.S. Patent No. 6,077,669, issued June 20, 2000, filed November 7, 1997), made in the Office Action mailed on June 1, 2005 is withdrawn in view of the Amendment received on January 17, 2006.

Specifically, the rejection is withdrawn in view of Applicants' specific arguments drawn to the fact that none of the references of record discloses a disposable unit having reagent wells of up to 1000 microns in depth defined between a thermally conducting layer and a facing layer.

The rejection of claims 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beutler et al. (U.S. Patent No. 5,234,811, issued August 10, 1993) in view of Kris et al. (U.S. Patent No. 6,238,869 B1, issued May 29, 2001, filed June 21, 1999) as evidenced by Heritz et al. (Journal of Urology, 1997, vol. 158, no. 6, pages 2291-2295) as applied to claims 1-4, 8, 14-16, 18, 25, and

---

amendment received on January 17, 2006, since non-responsive holdings based on formality does not require the

further in view of Danssaert et al. (U.S. Patent No. 5,525,300, issued June 11, 1996), made in the Office Action mailed on June 1, 2005 is withdrawn in view of the Amendment received on January 17, 2006.

Specifically, the rejection is withdrawn in view of Applicants' specific arguments drawn to the fact that none of the references of record discloses a disposable unit having reagent wells of up to 1000 microns in depth defined between a thermally conducting layer and a facing layer.

Rejections, Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-5, 8-18, 21, 25-29, 32, and 33 under 35 U.S.C. 103(a) as being unpatentable over Beutler et al. (U.S. Patent No. 5,234,811, issued August 10, 1993) in view of Ronchi (U.S. Patent No. 6,372,484 B1, issued April 16, 2002, filed January 21, 2000, priority, January 25, 1999) as evidenced by as evidenced by Heritz et al. (Journal of Urology, 1997, vol. 158, no. 6, pages 2291-2295), made in the Office Action mailed on June 1, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on January 17, 2006 have been fully considered but they are not found persuasive for the reasons discussed in the, "Response to Arguments" section.

Applicants to submit an entirely new response having all parts, but rather parts which corrects the deficiency.

The Rejection:

Beutler et al. disclose a method of amplifying target nucleic acid, wherein said method involves the use of a buffer at pH of 8.8 (column 22, lines 26-42), said amplification reaction involving thermal cycling (column 22, lines 39-42).

The buffer system employs 670 µl (column 22, line 30) of 40 mM TrisHCl (column 21, line 20).

While Beutler et al. are silent on at what temperature the TrisHCl buffer is employed, it is a common knowledge that such buffer is employed at 25°C, as evidenced by Heritz et al., wherein the artisans conduct PCR amplification employing, "Tris-HCl pH 8.5 at 25°C."

Beutler et al. also employ 80 mg/ml solution of bovine serum albumin (column 22, lines 31-32).

Beutler et al. do not explicitly disclose that the amplification was conducted in a disposable unit that comprises a thermally conducting layer and a facing layer having one or more reagent wells of up to 1000 microns in depth, wherein the thermally conducting metal layer of the disposable unit is metal, or aluminum, or involves heat-sealing the facing layer and thermally conducting layer.

Ronchi discloses an apparatus comprising a facing layer and a backing layer, a well formed therebetween (column 5, lines 36-38), wherein the facing layer is sealed (column 5, lines 48-49). The backing layer, in an alternative embodiment is made of polymeric materials, such as polypropylene, polyethyelene, etc. (column 6, lines 22-27). Based on such disclosure, one of ordinary skill in the art would readily recognize that polystyrene would also be useful as a backing layer. The depth of the well formed between the facing layer and the backing layer is disclosed as being in the range of 0.25 mm to 1.27 mm, which is within 1000 microns (column 6, lines 40-44).

The reagent wells are disclosed as being filled via channel 36 (Figure 2), a single opening, through use of a pipett. The use of pipett fully meets the use of air pressure to force liquid into the device of Ronchi.

With regard to claims 9 and 10, Ronchi discloses that aluminum blocks are used to sandwich the device on Ronchi for the benefit of even heat distribution (column 8, lines 64-66).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of teachings of Beutler et al. and Ronchi to arrive at the invention as claimed for the following reasons.

Conducing PCR in a closed environment as been well-established in the art of amplification for the benefit of sealing-in the vapor produced during thermal cycling events, precluding loss of sample volume and the possibility of contamination of PCR products via vaporization of the sample fluid during amplification cycle. Hence, one of ordinary skill in the art at the time the invention was made would have been motivated to employ the PCR reaction involving the reaction conditions of Beutler et al. in a closed, sealed environment disclosed by Ronchi, for the advantage of conducting PCR in a sealed environment with a reasonable expectation of success.

While Ronchi does not disclose a backing layer that is made of metal, particularly, aluminum, *covered* with polymeric materials, *per se*, Ronchi sandwiches a sealed PCR chamber made of polymeric material between aluminum blocks, producing a functional identical structure. Ronchi, in doing this, explicitly discloses the advantage of using aluminum heat blocks, that is, even heat distribution (column 6, lines 61-65). Therefore, one of ordinary skill in the art would have been clearly motivated to produce a structure produced by Ronchi, but in an integrated way with a reasonable expectation of success.

With regard to kit claims 27 and 28, it would have been further obvious to package the reagents employed in the method of Beutler et al. with the device of Ronchi in view of the conventionality of kits in the analytical arts for the advantages of convenience, cost-effectiveness, matched and/or preweighed components, etc.

With regard to claim 5, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the teachings of Beutler et al., Ronchi., and Heritz et al., to conduct an empirical determination at arriving at optimal conditions required for amplifying a target nucleic acid via PCR.

Absent secondary characteristic showing unexpected/superior result, it is well-within the purview of an ordinarily skilled artisan to empirically determine what parameters must be controlled for optimally amplifying a target nucleic acids. Such parameters comprises, the length and the identity of primers involved, the G-C content, the melting temperature of the target nucleic acid, magnesium concentrations, PCR buffer concentration. This is evident in the various PCR conditions employed by Beutler et al. (columns 23 and 24).

MPEP 2144.05(II)(A) discloses that, "differences in concentrations or temperature ***will not support*** patentability of subject matter encompassed by prior art unless there is evidence indicating such concentration or temperature is critical," citing *In re Aller,* F.2d 454, 456, 105 USPQ 233, 235, (CCPA 1995).

Therefore, the invention as claimed is obvious over the cited references.

Response to Arguments:

Applicants traverse the rejection of the claims on the basis that none of the references teach or suggest "conducting an amplification reaction in a disposable unit, wherein the disposable unit comprises a thermally conducting layer and a facing layer having one or more reagent wells of up to

1000 microns in depth, as recited in pending Claim 1." (page 12, bottom paragraph; *underline*, original).

This assertion appears to be incorrect since it was specifically pointed out that Ronchi discloses an apparatus comprising a facing layer and a backing layer, a well formed therebetween (column 5, lines 36-38), wherein the facing layer is sealed (column 5, lines 48-49). The backing layer, in an alternative embodiment is made of polymeric materials, such as polypropylene, polyethyelene, etc. (column 6, lines 22-27). Based on such disclosure, one of ordinary skill in the art would readily recognize that polystyrene would also be useful as a backing layer. The depth of the well formed between the facing layer and the backing layer is disclosed as being in the range of 0.25 mm to 1.27 mm, which is within 1000 microns (column 6, lines 40-44).

Whether something is deemed "disposable" or not is a relative term as all things are to some degree, "disposable."

Clearly, indeed disclose a device having wells having the depth of up to 1000 microns.

Applicants contend that one of ordinary skill in the art would not have been motivated to combine the teachings of the artisans of record because the PCR reactions of Beutler et al. employs a DNA thermal cycler, which, "typically requires the use of a tube (microcentrifuge)." (page 13, bottom paragraph, Response).

Applicants further contend that the PCR machine of the type used by Beutler et al. employs a heat-conducting container for holding a given number of tubes, preferably 500 µl tubes (page 13, bottom paragraph, Response).

Applicants, thus conclude that one of ordinary skill in the art would not have been motivated to employ the teachings of Beautler et al. and Ronchi et al. for the advantage of conducting PCR in a sealed environment with a reasonable expectation of success because Beautler

et al. alone discloses a PCR reaction in a closed environment (a tube) without arriving at the claimed subject matter (page 14, 1st paragraph, Response).

Applicants' arguments are not found convincing for the following reasons.

The teachings of Beutler et al. relied upon by the rejection was for the PCR conditions, which is employed in at least the method of claim 1.

The full scope of Claim 1 (since Applicants' arguments appears to focus on claim 1) is drawn to a method, which comprises the steps of:

a) supplying to a reagent well in a disposable unit a reaction mixture comprising:

i) a sample which contains or is suspected of containing a target nucleic acid;

ii) primers, nucleotides, and enzymes required to effect amplification reaction; and

iii) a buffer system, wherein the disposable unit comprises a thermally conducting layer and a facing layer having one or more reagent wells of up to 1000 microns in depth defined therebetween; the reaction mixture comprising at least ***one*** of the following:

A) a buffer system wherein pH is above 8.3;

B) a detergent; and/or

C) a blocking agent.

The teachings of Beutler et al., relied on in the rejection of record was to provide the teachings for a PCR reaction system, wherein the artisan expressly employ a buffer at pH of 8.8 (column 22, lines 26-42).

The artisans disclose a known PCR reaction buffer conditions, wherein the buffer system employs 670 µl (column 22, line 30) of 40 mM TrisHCl (column 21, line 20).

It was also pointed out in the rejection that while Beutler et al. were silent on at what temperature the TrisHCl buffer was employed, it was a common knowledge that such buffer is

typically employed at 25°C, as evidenced by Heritz et al., wherein the artisans conduct PCR amplification employing, "Tris-HCl pH 8.5 at 25°C."

To reiterate, the teachings of Beutler et al. was relied on to the extent that one of ordinary skill in the art at the time the invention was made was clearly aware of the buffer conditions which the claims recited, or in the alternative, well-within the purview of an ordinarily skilled artisan to arrive at such a condition under optimization of well known and established reagent conditions.

Whether one of ordinary skill in the art would have been motivated to employ the unit disclosed by Ronchi was based on the motivation that when conducing PCR in a closed environment, one of ordinary skill in the art would have been motivated to seal-in the vapor produced during thermal cycling events, thereby precluding loss of sample volume and the possibility of contamination of PCR products via vaporization of the sample fluid during amplification cycle. As Applicants correctly state, the tubes which are typically used in PCR thermocycler are do not completely seal-in the mixture in the tube, which allows for vaporization for the mixture during the temperature cycles, thus allowing for loss of mixture volume, contamination to occur.

Therefore, it is maintained that one of ordinary skill in the art at the time the invention was made would have been motivated to employ the PCR reaction involving the reaction conditions of Beutler et al. in a closed, sealed environment disclosed by Ronchi, for the advantage of conducting PCR in a sealed environment with a reasonable expectation of success.

On page 14, 2nd paragraph of the Response, Applicants state that there is no motivation for one of ordinary skill in the art to use the reaction mixture of Beutler et al. which comprises BSA or higher than exemplary buffer pH (pH 8.8) in a PCR reaction mixture.

This statement is confusing because the prior art of record is simply disclosing that conditions for PCR reactions, such as that of Applicants' are known and taught.

Applicants claims simply require at least one (thus in the broadest embodiment, a single condition) of the three conditions, two of which are taught by Beutler et al. (BSA and pH of the buffer).

Were Applicants' assertion to be correct, a claim drawn to a method involving some device, which is known, and a PCR condition, which is also known, would be patentable because there is no motivation to combine the two teachings. This is simply not so. Although there are exceptions such as when the combination of the device and the specific reaction condition produces effects which merit secondary consideration (i.e., unexpected results), absent such evidence and clearly convincing fact, combination of old known parameters, such as that of the instant claims are deemed obvious.

With regard to Applicants' assertion that the specific type of disposable unit recited in Claim 1 overcomes the problems associated with conducting an amplification reaction in the disposable unit (page14, 4th paragraph, Response), lines 20-26 of the specification describes generally that the disclosed invention improves the prior art techniques, but does not address how the parameters of the claims are improving the prior art techniques. This type of generalized statements are found in most of patent specifications. If Applicants are intending to specify exactly what conditions produce such a "surprising" results (page 2, line 28), Applicants are encouraged to recite those limitations responsible for the results into the claim language for consideration.

With regard to Applicants' arguments drawn to the device of Ronchi having a single PCR chamber, while it is unclear what Applicants are arguing, if Applicants are contending that Ronchi

only discloses a single "well," (page 15, 2nd paragraph, Response), Applicants are reminded that instant claim recites that the disposable unit comprises having, "***one*** or more reagent wells."

The rejection is maintained therefore.

The rejection of claim 6 under 35 U.S.C. 103(a) as being unpatentable over Beutler et al. (U.S. Patent No. 5,234,811, issued August 10, 1993) in view of Ronchi (U.S. Patent No. 6,372,484 B1, issued April 16, 2002, filed January 21, 2000, priority, January 25, 1999) as evidenced by as evidenced by Heritz et al. (Journal of Urology, 1997, vol. 158, no. 6, pages 2291-2295), as applied to claims 1-5, 8-18, 21, 25-29, 32, and 33 above, and further in view of Moss et al. (U.S. Patent No. 5,386,021, issued January 31, 1995), made in the Office Action mailed on June 1, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on January 17, 2006 have been fully considered but they are not found persuasive for the reasons discussed in the, "Response to Arguments" section.

The Rejection:

The teachings of Beutler et al., Kris et al., and Heritz et al. have already been discussed.

The above-artisans do not disclose a method of amplification involving detergent reagent, particularly in the concentration of 0.1% v/v.

Moss et al. disclose a method of amplifying a target nucleic acid via PCR, employing 0.1% Tween reagent (column 12, lines 12-17).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Beutler et la., Ronchi, and Heritz et al. with the

teachings of Moss et al., combining commonly employed PCR reagents for the claimed method of amplification for the following reasons.

The art of PCR amplification is a well-established art (see filing date of Moss et al.).

MPEP 2144.05(II)(A) discloses that, "differences in concentrations or temperature ***will not support*** patentability of subject matter encompassed by prior art unless there is evidence indicating such concentration or temperature is critical," citing *In re Aller,* F.2d 454, 456, 105 USPQ 233, 235, (CCPA 1995).

Hence, absent secondary characteristic showing unexpected/superior result, it is well-within the purview of an ordinarily skilled artisan to empirically determine what parameters must be controlled and reagents must be involved for optimally amplifying a target nucleic acids. Such parameters comprises, the length and the identity of primers involved, the G-C content, the melting temperature of the target nucleic acid, magnesium concentrations, detergent concentrations, PCR buffer concentration, rendering the invention as claimed obvious over the cited references.

Therefore, the invention as claimed is obvious over the cited references.

Response to Arguments:

All of Applicants' arguments are drawn to the rejection of claim 1 (of record), which have been fully addressed above.

Since Applicants do not present any new arguments for the instant rejection, the rejection is maintained for the reasons of record.

The rejection of claims 19, 20, 30, and 31 under 35 U.S.C. 103(a) as being unpatentable over Beutler et al. (U.S. Patent No. 5,234,811, issued August 10, 1993) in view of Ronchi (U.S. Patent No. 6,372,484 B1, issued April 16, 2002, filed January 21, 2000, priority, January 25, 1999) as evidenced

by as evidenced by Heritz et al. (Journal of Urology, 1997, vol. 158, no. 6, pages 2291-2295), as applied to claims 1-4, 8-18, 21, 25-29, 32, and 33 above, and further in view of Little et al. (U.S. Patent No. 6,077,669, issued June 20, 2000, filed November 7, 1997), made in the Office Action mailed on June 1, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on January 17, 2006 have been fully considered but they are not found persuasive for the reasons discussed in the, "Response to Arguments" section.

The Rejection:

The teachings of Beutler et al., Ronchi, and Heritz et al. have already been discussed above.

The above artisans do not explicitly teach that the reagents could be predosed in dried forms in at least one disposable unit having a plurality of wells.

Little et al. disclose a well-known method of providing reagents in a dried form in a disposable device (column 2, lines 30-34).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide the reagents of Beutler et al., Ronchi, and Heritz et al. in their dried forms in the wells of a disposable device in order to provide devices comprising matched and preweighed reagents, for the obvious advantage of reducing contamination, and eliminating the time consuming steps of adding appropriate amounts of reagents for reactions to occur.

Therefore, the invention as claimed is obvious over the cited references.

Response to Arguments:

Applicants' initial arguments drawn to the rejection of claim 1 (of record) have been fully considered and fully addressed in the above response.

With regard to Applicants' contention that Little et al. teaches away from the combination because, "the use of dried reagents 'has been found to cause an unreproducible fluorescence detection signal'" (page 17, 2nd paragraph, Response), Applicants' statement is taking the disclosure out of context and mischaracterizing the disclosure.

Little states the following:

> of the method). However, the rehydration of all dried nucleic acid amplification reagents and all dried nucleic acid probe assay reagents at essentially the same time has been found to cause an unreproducible fluorescence detection signal. This unreproducible signal is believed to be due to variable rehydration of the fluorescently labeled dried nucleic acid probe, and causes interference with the desired fluorescence signal, which interference cannot be factored out, because of the unreproducible nature of the interfering signal. Also, the

Clearly, the "unreproducible fluorescence detection signal" is arising from the pre-dried nucleic acid probes which are labeled.

The claims of the instant application do not require a pre-dosed, dried nucleic acid probe which are labeled.

Thus, one of ordinary skill in the art would have been motivated to dispose pre-dosed, dried amplification reagents, for the sake of convenience and precluding contamination by opening and closing the device in the process of adding requisite reagents.

Applicants are also referred to WO 98/09728, page 17, lines 14-15), which is prior art that was published a year before the effective filing date of the application.

The rejection is maintained therefore.

The rejection of claims 22-24 under 35 U.S.C. 103(a) as being unpatentable over Beutler et al. (U.S. Patent No. 5,234,811, issued August 10, 1993) in view of Ronchi (U.S. Patent No. 6,372,484 B1, issued April 16, 2002, filed January 21, 2000, priority, January 25, 1999) as evidenced by as evidenced by Heritz et al. (Journal of Urology, 1997, vol. 158, no. 6, pages 2291-2295), as applied to claims 1-4, 8-18, 21, 25-29, 32, and 33 above, and further in view of Danssaert et al. (U.S. Patent No. 5,525,300, issued June 11, 1996), made in the Office Action mailed on June 1, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on January 17, 2006 have been fully considered but they are not found persuasive for the reasons discussed in the, "Response to Arguments" section.

The Rejection:

The teachings of Beutler et al., Ronchi and Heritz et al. have already been discussed above.

The above artisans do not explicitly teach the disposable unit being placed in an apparatus comprising at least two heating blocks.

Danssaert et al. disclose an apparatus comprising multiple heating blocks, said apparatus comprising: a) a plurality of reaction blocks (Figure 1, components 3, 17, 18, and 19), wherein at least one of the blocks is a heat reaction block and at least one of the blocks is a cold reaction block (Figure 3), wherein a reaction vessel (Figure 1, component 20) has a plurality of openings formed therein; b) a robotic arm which transfers the reaction vessels from one hot reaction block to one cold reaction block (Figure 1; column 1, lines 29-35; column 4, lines 35-42; column 5, lines 42-45); and c) a controller having a user interface for inputting temperature and sampling interval, the controller in communication with the blocks and robotic device (column 5, lines 25-42). The apparatus of Danssaert et al. conducts PCR (polymerase chain reaction) which is considered to be

non-isothermal reaction (column 7). With regard to the apparatus of Danssaert et al., as well as most of the thermocycler, display the cycle times and their corresponding temperature at said cycle (Figure 1, component 16).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Beutler et al., Ronchi and Heritz et al. with the apparatus of Danssaert et al. for the advantage of determining the optical temperatures required in a PCR reaction (column 3, lines 5-8, Danssaert et al.).

Therefore, the invention as claimed is obvious over the cited references.

Response to Arguments:

All of Applicants' arguments are drawn to the rejection of claim 1 (of record), which have been fully addressed above.

Since Applicants do not present any new arguments for the instant rejection, the rejection is maintained for the reasons of record.

Rejections, New Grounds

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 8-12, 14, 15, 16, 18, 21, 22, 25-29, 32, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Wilding et al. (U.S. Patent No. 5,587,128, issued December 24, 1996).

For the purpose of clarity, the present rejection is divided in two parts (The Method and The Device).

The Method: (claims 1, 2, 8-12, 14, 15, 16, 18, 21, 22, 25, and 26)

Wilding et al. disclose a single-use device (thus disposable; see column 1, lines 22-23; column 9, lines) for conducting thermal cycling reaction (column 1, lines 24-25), comprising a thermally conducting layer (aluminum; see column 14, lines 24-31) and a facing layer having a plurality of reagent wells (column 4, lines 42-44), wherein all the reagent wells are fed by a common channel (column 4, lines 24-26) which includes a single opening to the outside of the unit (column 4, lines 19-20), wherein the depth of the chambers is disclosed as being in the range of 0.1 to 1000 μm (column 4, lines 46-48).

In describing the method of using the above device in a PCR reaction, the artisans explicitly disclose that the PCR is conducted with a reaction mixture comprising at least the Tris buffer at pH 8.6 (see column 27, lines 35-36), having dissolved therein, a blocking agent (column 27, line 24), said blocking agent being BSA (column 16, line 22), thereby clearly anticipating claims 1, 2, 8, 9, 10, 14, and 21.

With regard to claims 11, 12, and 15, the metal substrate is disclosed as being coated with a biocompatible layer (column 5, line 55 through column 6, line 2), in an embodiment, polystyrene (column 7, lines 34-36).

With regard to claim 16, as evidenced by Figure 7, the device comprises holes and channels which define reagent wells and channels adhered between the thermally conducing layer and the facing layer.

With regard to claim 18, as evidenced by Figure 7, there is a spacer means (i.e., wall) which is provided within each well.

With regard to claim 25, in the method of amplification, the artisans disclose that the temperatures of one or more chambers are regulated by providing one or more electrical resistant heaters in the substrate near the reaction chambers (column 8, lines 28-32).

With regard to claim 26, the presence of labeled reagents within the disposable unit is monitored (column 8, lines 47-59).

The Device: (claims 27-29, 32, and 33)

Wilding et al. disclose a single-use device (thus disposable; see column 1, lines 22-23; column 9, lines) for conducting thermal cycling reaction (column 1, lines 24-25), comprising a thermally conducting layer (aluminum; see column 14, lines 24-31) and a facing layer having a plurality of reagent wells (column 4, lines 42-44), wherein all the reagent wells are fed by a common channel (column 4, lines 24-26) which includes a single opening to the outside of the unit (column 4, lines 19-20), thereby clearly anticipating claims 28, 29 and 32.

The depth of the chambers is disclosed as being in the range of 0.1 to 1000 μm (column 4, lines 46-48).

With regard to claim 33, the disposable unit is filled with a liquid by use of a syringe which injects the sample in to the device (syringe employs air pressure; column 7, lines 47-48).

With regard to claim 27, the PCR condition conducted in the disposable device comprises Tris buffer at pH 8.6 (see column 27, lines 35-36).

Therefore, Wilding et al. clearly anticipate the invention as claimed.

Claim Rejections - 35 USC § 103

Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilding et al. (U.S. Patent No. 5,587,128, issued December 24, 1996) in view of Beutler et al. (U.S. Patent No.

5,234,811, issued August 10, 1993) as evidenced by Heritz et al. (Journal of Urology, 1997, vol. 158, no. 6, pages 2291-2295).

The teachings of Wilding et al. have already been disclosed above.

Wilding et al. do not explicitly recite the PCR reaction condition which is recited in claims 3-5.

Beutler et al. disclose a method of amplifying target nucleic acid, wherein said method involves the use of a buffer at pH of 8.8 (column 22, lines 26-42), said amplification reaction involving thermal cycling (column 22, lines 39-42).

The buffer system employs 670 µl (column 22, line 30) of 40 mM TrisHCl (column 21, line 20).

While Beutler et al. are silent on at what temperature the TrisHCl buffer is employed, it is a common knowledge that such buffer is employed at 25°C, as evidenced by Heritz et al., wherein the artisans conduct PCR amplification employing, "Tris-HCl pH 8.5 at 25°C."

Beutler et al. also employ 80 mg/ml solution of bovine serum albumin (column 22, lines 31-32).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Wilding et al. and the teachings of Beutler et al. and Heritz et al., thereby arriving at the claimed invention for the following reasons.

Conducing PCR in a closed environment as been well-established in the art of amplification for the benefit of sealing-in the vapor produced during thermal cycling events, precluding loss of sample volume and the possibility of contamination of PCR products via vaporization of the sample fluid during amplification cycle. Hence, one of ordinary skill in the art at the time the invention was made would have been motivated to employ the device of Wilding et al., that is a closed, sealed

environment disclosed by for the advantage of conducting PCR in a sealed environment, wherein the determination of buffer conditions and requisite requirements employed therein would have been determined by procedures involving optimization of routinely employed conditions.

Conducting empirical determination at arriving at optimal conditions required for amplifying a target nucleic acid via PCR, absent secondary characteristic showing unexpected/superior result, is well-within the purview of an ordinarily skilled artisan. Such conditions comprises, the length and the identity of primers involved, the G-C content, the melting temperature of the target nucleic acid, magnesium concentrations, PCR buffer concentration.

MPEP 2144.05(II)(A) discloses that, "differences in concentrations or temperature ***will not support*** patentability of subject matter encompassed by prior art unless there is evidence indicating such concentration or temperature is critical," citing *In re Aller,* F.2d 454, 456, 105 USPQ 233, 235, (CCPA 1995).

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable Wilding et al. (U.S. Patent No. 5,587,128, issued December 24, 1996) in view Moss et al. (U.S. Patent No. 5,386,021, issued January 31, 1995).

The teachings of Wilding et al. have already been discussed above.

Wilding et al. do not explicitly disclose a method of amplification involving detergent reagent, particularly in the concentration of 0.1% v/v.

Moss et al. disclose a method of amplifying a target nucleic acid via PCR, employing 0.1% Tween reagent (column 12, lines 12-17).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Wilding et al. with the teachings of Moss et al., combining commonly employed PCR reagents for the claimed method of amplification for the following reasons.

The art of PCR amplification is a well-established art (see filing date of Moss et al.).

While Wilding et al. does not include all possible reagents involved in amplification reactions, one of ordinary skill in the art at the time the invention was made would have been motivated to include the amount and combination of reagents necessary known in the art, so as to arrive at the amplification reaction condition which produces optimal results with a reasonable expectation of success.

MPEP 2144.05(II)(A) discloses that, "differences in concentrations or temperature ***will not support*** patentability of subject matter encompassed by prior art unless there is evidence indicating such concentration or temperature is critical," citing *In re Aller,* F.2d 454, 456, 105 USPQ 233, 235, (CCPA 1995).

Hence, absent secondary characteristic showing unexpected/superior result, it is well-within the purview of an ordinarily skilled artisan to empirically determine what parameters must be controlled and reagents must be involved for optimally amplifying a target nucleic acids. Such parameters comprises, the length and the identity of primers involved, the G-C content, the melting temperature of the target nucleic acid, magnesium concentrations, detergent concentrations, PCR buffer concentration, rendering the invention as claimed obvious over the cited references.

Therefore, the invention as claimed is obvious over the cited references.

Claims 19, 20, 30, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilding et al. (U.S. Patent No. 5,587,128, issued December 24, 1996) in view of Corless et al. (WO 98/09728, published March 12, 1998).

The teachings of Wilding et al. have already been discussed above.

Wilding et al. do not explicitly disclose that the method of amplification involves a device whose chambers are predosed with dried reagents (claims 19 and 30), wherein the dried reagents are PCR reagent primers or probes (claims 20 and 31).

Corless et al. discloses a well known concept of employing predosed, dried reagents in a disposable amplification device (see page 17, lines 14-15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide the reagents of Wilding et al. in their dried forms in the wells of a disposable device in order to provide devices comprising matched and preweighed reagents, for the obvious advantage of reducing contamination, and eliminating the time consuming steps of adding appropriate amounts of reagents for reactions to occur.

Therefore, the invention as claimed is obvious over the cited references.

Claims 13 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilding et al. (U.S. Patent No. 5,587,128, issued December 24, 1996) in view of Dubrow et al. (U.S. Patent No. 6,488,897, issued December 2, 2002, filed May 1, 2001, priority February 24, 1998).

The teachings of Wilding et al. have already been discussed above.

Wilding et al. do not explicitly disclose that the facing layer and thermally conducing layer are adhered together by a biocompatible adhesive (claim 17) or heat sealed together (claim 13).

Dubrow et al. evidences various well known methods of creating microfluidic devices, wherein the method involves bonding via adhesives (column 9, lines 10-20).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to derive at the device of the Wilding et al. by variously well-known methods of micromachining techniques, such as heat-sealing or via use of a biocompatible adhesive materials.

It is expressly asserted that methods of heat-sealing or use of adhesive to attach different layers so as to form reaction chambers is well known and established in the art of microfluidics and micromachining, as evidenced by Dubrow et al.

Given the structure of Wilding et al., one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at employing any of the well known techniques, so as to arrive at the device of Wilding et al., rendering the claims obvious over the cited references.

Claims 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilding et al. (U.S. Patent No. 5,587,128, issued December 24, 1996) in view of Danssaert et al. (U.S. Patent No. 5,525,300, issued June 11, 1996).

The teachings of Wilding et al. have already been discussed above.

Wilding et al. do not explicitly teach the disposable unit being placed in an apparatus comprising at least two heating blocks.

Danssaert et al. disclose an apparatus comprising multiple heating blocks, said apparatus comprising: a) a plurality of reaction blocks (Figure 1, components 3, 17, 18, and 19), wherein at least one of the blocks is a heat reaction block and at least one of the blocks is a cold reaction block (Figure 3), wherein a reaction vessel (Figure 1, component 20) has a plurality of openings formed therein; b) a robotic arm which transfers the reaction vessels from one hot reaction block to one

cold reaction block (Figure 1; column 1, lines 29-35; column 4, lines 35-42; column 5, lines 42-45); and c) a controller having a user interface for inputting temperature and sampling interval, the controller in communication with the blocks and robotic device (column 5, lines 25-42). The apparatus of Danssaert et al. conducts PCR (polymerase chain reaction) which is considered to be non-isothermal reaction (column 7). With regard to the apparatus of Danssaert et al., as well as most of the thermocycler, display the cycle times and their corresponding temperature at said cycle (Figure 1, component 16).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Wilding et al. with the apparatus of Danssaert et al. for the advantage of determining the optimal temperatures required in a PCR reaction (column 3, lines 5-8, Danssaert et al.).

Therefore, the invention as claimed is obvious over the cited references.

Conclusion

Claims 34 and 35 are free of prior art as there is no motivation to employ the method of claims to fill the disposable unit defined in the claims.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts

to reach the above Examiners are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Patent Examiner
Art Unit 1637
5/1/2006

yjk